



## (WO/1999/053030) METHOD AND SYSTEM FOR MANAGING IMMUNOCOMPETENT CELL BATCHES FOR DELAYED USE

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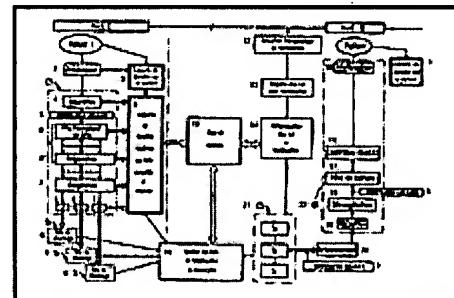
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Title: (EN) METHOD AND SYSTEM FOR MANAGING IMMUNOCOMPETENT CELL BATCHES FOR DELAYED USE  
 (FR) PROCEDE ET SYSTEME DE GESTION DE LOTS DE CELLULES IMMUNO-COMPETENTES EN VUE D'UTILISATIONS DIFFERES

Abstract: (EN) The invention concerns a method for managing immunocompetent cell batches belonging to human subject from whom said sets have been removed for future use on said subjects or relatives. Each immunocompetent cell batch associated with a subject is packaged and stored in a cryogenic site among a plurality of cryogenic sites, then transferred on request to a cell treatment centre. Said method provides individual preservation of immunocompetent elements and the possibility, if it is so desired, of culturing them with growth thereof. It aims at protecting the immunity and genetic capital from being altered during the individual's lifetime. The invention is particularly useful for reinforcing immune activity and gene therapy.



(FR) Procédé pour gérer des lots de cellules immuno-compétentes appartenant à des sujets humains sur lesquels ces lots ont été prélevés en vue d'une utilisation différée sur ces sujets ou sur des parents. Chaque lot de cellules immuno-compétentes associé à un sujet est conditionné et stocké dans un site de stockage cryogénique parmi une pluralité de sites de stockage cryogénique, puis transféré à la demande depuis ce site de stockage vers un centre de traitement cellulaire. Ce procédé procure une préservation individuelle d'éléments immuno-compétents et la possibilité d'en faire, si on le désire, une culture avec une croissance. Il s'agit de préserver le capital immunitaire et génétique de toute altération, au cours de la vie de l'individu. Utilisation notamment pour le renforcement de l'activité immunitaire et en thérapie génique.

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**(WO/1999/053030) METHOD AND SYSTEM FOR MANAGING IMMUNOCOMPETENT CELL BATCHES FOR DELAYED USES****Biblio. Dated Description Claims National Phase Notes Documents**

"PROCEEDED AND SYSTEM OF MANAGEMENT OF BATCHES OF CELLS IMMUNO-COMPÉTENTES FOR DIFFERED USES" the present invention relates to a process of management of batches of immuno-qualified cells, in particular of lymphocytes or monocytes, for differed uses. It also aims a system of management for the implementation of the process according to the invention.

Scientific and clinical work highlighted the therapeutic virtues of the car-use of derived lymphocytaires and monocytaires which contributes in particular to an increase in cellular immunity.

A promising application of this therapeutic method relates to the possibility of reinforcing the immunity of a patient at one time of his life where this reinforcement proves to be necessary or vital or to maintain this immunity with the wire of its life.

However, a difficulty important to surmount lies in the availability of the lymphocytes or monocytes of a patient over periods of times which could tre ranging between several months and several tens of years. One knows already techniques of cryogenic storage from now on largely used in many fields of human and animal biology. Banks were in particular installation for the conservation and the storage of biological elements.

The W089/04168 document reveals a process of insulation and conservation of hematopoietic cells of foetal blood and néonatal. This process aims in particular the therapeutic use of foetal cells and néonatales for hematopoietic reconstitutions or in genic therapy, and can tre implemented for the cryo-conservation of cells of foetal blood or néonatal at ends of reconstitution autologist.

Cells immuno-qualified (lymphocytes, phagocytic cells: monocytes, macrophages) play a central part in the immune system. In particular, the lymphocytes store information during the life and are the storage medium of cellular immunity and humorale.

This library, lymphocitary in particular, but also 1 ' whole of the immune system, grows rich during the life, as the individual meets foreign organizations, during the viral, parasitic or bacterial infections. It is grace-with it that the organization can minimize the impact of the infections during the life. The mechanism of action of cellular immunity is known. Information is in particular stored in the walls of the lymphocytes, as the factor of transfer and many publications shows it. This mechanism also contributes to defense against the malignant cells.

On the one hand, this memory is erased partly with time, as the need shows it for practising recalls of vaccination to preserve an effective protection. With regard to immunity humorale, the rates of antibody drop, quickly for IgM, more slowly for IgG and IgA.

In addition, of the errors are introduced with time and immunity becomes often less effective with the years. It is because of this degradation that infections comme' the influenza are much more serious at the old people. There would be thus intérêt to be able to store the acquired information all during the life.

The taking away can take place at any age, as soon as the immune system is mature, either by peripheral blood test, or by leucophérèse, or by taking away of marrow. These taking away store a more important information, since they are complete and alive cells, that that transmitted by the factor of transfer which is only one extract of lymphocitary wall. The considerable value of the factor of transfer is largely proven.

However, it proves that the current infrastructures and methods storage management of biological batches are not adapted to the specific application of the car-injection differed in the long run which requires a management in the very long term of the batches of immuno-qualified cells.

The goal of the invention is to propose a process to manage batches of immuno-qualified cells, which makes it possible to store the acquired information all during the life, with a full cover of storage and availability in the very long

term.

There this objective is achieved by storing cells of the immune system at various periods of the life to be able to appeal later where necessary, in particular: - occurred of a not controlled acute infection, - persistence of a chronic infection, - appearance of a malignant disease, - appearance of a disease concerning the immune system him-Mrs., - prevention of these diseases at a receiver centre.

According to the invention, the process of management of batches of immuno-qualified cells includes/understands, for a given human subject: - a conditioning and a storage of the batches of immuno-qualified cells in one or more centers of storage, - a constitution and an enrichment of a personal library of immuno-qualified cells starting from the successively taken batches, this personal library preserving a sum of immunizing information stored in the taken immuno-qualified cells, and, response to a reque of treatment the of the aforesaid profit prone human: - a treatment of whole or part of the immunizing information accumulated in the aforementioned personal library, and - a localization of one or more stored batches of immuno-qualified cells, followed by a transfer of this or these batches towards a cellular processing center requiring.

The process of management according to the invention can moreover comprise a plan of taking away of the batches of immuno-qualified cells with various stages of the life of each human subject profiting from this process.

This plan of taking away can comprise stages of taking away at predetermined ages of the human subject, as well as not programmed stages of taking away conditioned by particular events of the life of the human subject.

Thus, with the process according to the invention, it becomes possible to preserve the immunizing and genetic capital of any deterioration during the life of an individual by carrying out an individual conservation of immuno-qualified elements with faculty to make some, if it is wished, a culture with a growth.

It is indeed possible to defrost an aliquot part of the immuno-qualified or immunizing cells preserved, to cultivate them, stimulate their functions for example with the interleukine 2 or the interleukine 12, then to reinject them with the patient, that is to say by venous, or lymphatic, or local way. The therapeutic effect can tre fast. This process is not invasive. It does not introduce foreign cells into the organization, since they are cells autologists. There is not thus to fear phenomenon of rejection, systems HLA being compatible.

The conservation of these cells also allows a differed genetic analysis which, by comparison, can reveal changes which have occurred meanwhile. The conservation of plasma can also make it possible to find the trace of unknown infections at the time of the taking away.

In a mode preferred of implementation of the process according to the invention, each batch of lymphocytes associated on a subject is conditioned and stored in a site of cryogenic storage among a plurality of sites of cryogenic storage, then transferred to the request since this site from storage towards a re-used cellular processing center for tre, and with each phase of taking away a collection is associated, on the one hand, personal data relating to the taken subject and on the other hand, data relating to the taking away.

Thus, such a process brings to the patients the guarantee of a conservation of their lymphocytes on the long term, with the prospect for being able to lay out about it constantly for amongst other things reinforcing their immune system. It then becomes possible to give again with the people their former immunity and to transmit a cellular immunity, under conditions of rational and reliable management, and moreover to have access to their genetic code corresponding to the date of taking away of blood.

Preferably, at the end of a phase of taking away, the taken lymphocytes are conditioned in the form of a plurality of batches of lymphocytes. This allows a flexible and effective management re-injections, without fear to have to defrost a batch of lymphocytes in excessive quantity compared to the specific needs.

Implementation an advantageous of the process according to the invention consists of what the batches of immuno-qualified cells are stored in several geographically distinct sites of cryogenic storage. This characteristic aims at increasing the safety of conservation of the taken lymphocytes or monocytes.

More generally, in the process of management according to the invention, the concept of differed use covers at the same time the field with the car-uses in the form in particular of car-injection, use of factor of transfer obtained starting from the lymphocytaires taking away, or of use of the monocytes, or use of culture of lymphocytes with growth promoters such as the interleukine 2, and the field of the uses of filiation, in particular in genic therapy, in particular the reading of the genetic code and the use of lymphocytes or monocytes taken on parents.

The batches of lymphocytes or monocytes can for example tre re-used after cellular culture in the presence of cellular

mediators, such as the interleukine 2, with the fine therapeutic ones.

According to another aspect of the invention, it is proposed a system to manage taking away of immuno-qualified cells, implementing the process according to the invention, this system being established in: - a plurality of centers of taking away and conditioning of batches of immuno-qualified cells, - a plurality of sites of cryogenic storage designed to receive the batches of immuno-qualified cells, - a plurality of cellular processing centers of batches of immuno-qualified cells, and - one or a plurality of centers of management of the batches of immuno-qualified cells, connected by means of communication to the centers of taking away, the sites of cryogenic storage and the cellular processing centers, characterized in that it includes/understands: - means to constitute and enrich, with/leave of the aforesaid successively taken batches, a personal library of immuno-qualified cells, this personal library preserving a sum of immunizing information stored in the taken immuno-qualified cells, - means to treat whole or part of the immunizing information accumulated in the aforementioned personal library, in response to a reque of treatment to the of the aforesaid profit prone human, - means to locate one or more stored batches of immuno-qualified cells, and - means to transfer this or these batches towards a cellular processing center requiring.

In a mode of advantageous realization, the system of management includes/understands moreover means to establish, for each human subject profiting of the aforesaid system, a plan of taking away of batches of immuno-qualified cells during its life, and of the means to transmit to one or more centers of taking away and conditioning of the instructions and information relating to the execution of the plan of taking away.

Preferably, the centers of management cooperate with a fast center of logistics to forward the batches of immuno-qualified cells since the sites of cryogenic storage to the cellular processing centers.

In addition, the system of management according to the invention includes/understands moreover means to collect personal data relating to the patients subjected to taking away of lymphocytes or monocytes in the plurality of centers of taking away.

Other characteristics and advantages of the invention will still appear in description hereafter. With the annexed drawings given as nonrestrictive examples: it figure 1 is a synoptic diagram of the process and system of management of lymphocytaires taking away according to the invention; it figure 2 illustrates respective flows of taking away, personal data and data of management, resulting from the implementation of the process of management according to the invention; and it figure 3 illustrates the relations between sites of re-injection, storage and management, within a system of management according to the invention.

One now will describe an example of implementation of the process of management of lymphocytaires taking away or monocytaires, in Mrs. time that the corresponding system of management, in reference on figure 1.

A first phase I relates to the taking away and the realization of the lymphocytaires batches or monocytaires.

The following stages are carried out at the time of a phase I carried out in a center specialized CT: - a data, data acquisition in particular relating to the tissue grouping, and information relating to a patient I, - a taking away of blood on this patient, - a treatment of taken blood and a separation of the lymphocytes and/or monocytes, - a cellular identification, - a fractionation to carry out a whole of batches of lymphocytes and/or monocytes, - a preparation of the lymphocytes and/or monocytes, including amongst other things, possibly a dehydration, - a congelation and setting in cryogenic storage of N batches of lymphocytes and/or monocytes Li, 1, Li, J, Li, N, in a system of refrigeration adapted, for example in a gas atmosphere of refrigeration.

It should be noted that the operations of separation and fractionation can be integrated and carried out within an apparatus with cytophérèse. In addition, the cellular stage of identification, which can implement various known techniques of identification, can intervene at other stages of phase I according to technical specificities.

The batches of frozen lymphocytes and/or monocytes are then distributed in various sites or banks of storage SA, SK, SL. Storages of batches of lymphocytes are made safe and managed. This management implements a data base supplied with data collected at the time of each phase of taking away and of storage I. the batches of immuno-qualified cells could thus be stored over very variable durations being able to go from a few days to several tens of years subject to the guarantee of a good conservation of the lymphocytes or monocytes on the long term. In addition, the principle of not storing the whole of the batches of a patient in Mrs. site contributes amply to the security of supply.

When a therapeutic indication concerning a patient having profited from this process of management recommends a use of lymphocytes or monocytes, one then undertakes phase II of the process. The company manager of the process is contacted and receives a reque for a batch of immuno-qualified cells stored and managed for the account of this patient. Thanks to the interrogation of the data base, one determines and one locates a batch pertaining to this patient in one of the sites of storage SA, SK, SL of the whole of sites ES.

After localization and cellular identification, the batch concerned is conveyed by fast transport until a cellular processing center CR which can be besides the center in which the initial taking away had been carried out.

The phase of re-use (for example, re-injection) includes/understands for example: - a reception of the batch including a control of identification which can in particular comprise a reading of code-bars and a tissue grouping, - a defrosting of the batch, - a new cellular identification, - a handing-over in suspension of the lymphocytes or monocytes in a culture medium, - check operations of quality and safety, and - a re-use of the lymphocytes in the patient.

At the time of this phase II of re-use, new data relating to the patient can be again collected at ends of studies and statistics treatment.

One now will describe the process of management in terms of flow, with an analysis of the transfers of elements biological, personal data and data relating to the taking away and storages, in reference on figure 2. From any patient calling upon one moment T1 with the services of a trust company of taking away, the transfers are carried out according to: - a transfer of biological elements consisted taken and separated lymphocytes LY or monocytes, - a transfer of personal data DP collected at the time of the taking away, subject to the respect of the specific legal provisions to each state, - a transfer of data and parameters directly associated the taking away and essential for the inventory control of taking away.

Each one of these types of transfer leads to processes of collection: - a collection of the batches of qualified cells immuno- with a centralized management and diversified sites of storage, - a personal data-gathering to feed from the statistical data bases, and - a data-gathering of taking away to constitute a data base of management of the batches of immuno-qualified cells.

When a phase II of re-use, for example in the form of a re-injection, is decided at one moment T1+AT, are carried out the following transfers: - a transfer of a batch of qualified cells immuno- since a site of storage towards a cellular processing center, - a transfer of the data and parameters associated with this batch, and - a transfer of personal data reactualized on this patient, which are collected at the time of the phase of re-use.

One now will describe the conditions of realization of a phase of re-use within the framework of the process of management according to the invention, more particularly in terms of geographical localization and logistics, in reference on figure 3.

On a given territory, which can be a continent, a state, an area, or a urban community, centers of cytophérèse or lymphocytic therapy CR1, CRK are set up. These centers, designed to receive patients pi, Pj, Px, Py having adhered to a program of taking away-re-use implementing the process of management according to the invention, are in communication by means of connection TL such as communication networks closed or opened (Internet) in centers MC of management of storages of lymphocytes or monocytes which can be localised in any point of the sphere. This center of management MC is in permanent communication by suitable means of communication SL (specialized connections or open network such as Internet) <BR> <BR> <BR> <BR> with the whole of the sites of storage SA, SL. In addition , the center of management MC cooperates with a fast center of logistics AI which controls a whole of platforms of fast forwarding APA, APL in the vicinity of which the sites of storage are preferably established. As example of implementation of the process of management according to the invention, a patient J contacts (1), on medical indication, a center of cytophérèse or re-use CR1 of his choice, for example the center nearest to at his place. The cellular processing center CR1 consults on a terminal connected to the center of management MC and (2) a requete of batch transmits to him. The center of management MC questions the data base of management and locates a batch of qualified cells immuno- Lj corresponding to this patient in one of the sites of storage. In the event of diversified multiple storage, the site of storage nearest to the cellular processing center CR1 is selected. The center of management MC transmits (3) the requete to the site of storage selected SA and contacts (4) the center it logistic rapid AI the site of storage SA extracts the batch concerned then and immediately to the platform fast forwarding APA transmits it which was activated beforehand (5) by the fast center of logistics AI the batch Lj is then conveyed (6) by average the rapids available, preferably by plane, bound for the cellular processing center CR1.

It should be noted that each patient adhering to such a program generally has a stock of batches of immuno-qualified cells which makes it possible for example to spread out in the time of the successive car-uses, for example in the form of car-injections, at ends of reinforcement of the immune system or genic or different therapy, or to massively use where necessary the stock of lymphocytes or monocytes thus made up.

The process of management according to the invention is preferably materialized in the form of a software established on systems of management and treatment of information which can be localised in centers of management of batches and be connected to a whole of local computer sites within the centers of cytophérèse, of fast logistics and storage.

Of course, the invention is not limited to the examples which have been just described and of many alterations can be

made to these examples without leaving the framework of the invention. Thus, one can envisage, within the framework of the phases of taking away and re-use, of the additional technical stages according to medical requirements and of constraints of safety. The means of communication implemented between the various operational centers and management can be of any nature.

In addition, the information collected within the framework of the process of management according to the invention can be advantageously treated with fine statistics, with applications in the field of the prevention and the insurance.